We should be considering lung cancer screening for never-smoking Asian-American females

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We should be considering lung cancer screening for never-smoking Asian-American females

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Glossary of Abbreviation:

LCS - Lung cancer screening

USPSTF - United States Preventive Services Task Force

LDCT - Low-dose computed tomography

TALENT - Taiwan Lung Cancer Screening for Never smoker Trial

NLST – National Lung Cancer Screening Trial

NELSON – Nederlands-Leuvens Longkanker Screening Onderzoek

NSF - Never-smoker females

NCCN- National Comprehensive Cancer Network

PLCO – Prostate, Lung, Colorectal, and Ovary

AAIR- Age-adjusted incidence rate

CHEST- American College of Chest Physicians

AATS- American Association for Thoracic Surgery

FPR- False positive rate

RADS – Reporting and Data System

GGN- Ground glass nodule

AAH - Atypical adenomatous hyperplasia
41 AIS - Adenocarcinoma in-situ
42 MIA - Minimally-invasive carcinoma
43 IAC - Invasive Adenocarcinoma
44 FANS - Female Asian Never Smoker Study
45 FANSS - Female Asian Non-smoker Screening Study

Central picture:

Central picture legend (90 characters incl spaces):
Do untreated low-grade neoplasms as on this CT, impact survival in Asian-American females?

Central message (200 characters incl spaces): Asian females – even with no cigarette exposure – have a sufficiently high risk of lung cancer that we must consider including them among groups recommended for lung cancer screening.

Perspective Statement (405 characters incl spaces): CT screening for lung cancer, as for all diseases, is most appropriate in the highest-risk patients. Lung cancer risk has focused on extent of smoking history, to the exclusion of other factors. There is an epidemic of lung cancer in Asian-Americans without a smoking history, particularly females. We argue that their risk is sufficiently high to consider recommending CT screening for this population.

Keywords: Lung neoplasms, Early detection of cancer, Asian American Native Hawaiian and Pacific Islander, Non-smokers, Females
Introduction to the problem

An estimated 250,000 new cases of lung cancer will be diagnosed in the USA alone in 2023\(^1\). Lung cancer has the highest cancer-related mortality, and early detection through lung cancer screening (LCS) is the most effective way to reduce mortality. Age and cigarette smoking have been the major inclusion criteria for LCS--the United States Preventive Services Task Force (USPSTF) recommends annual low-dose computed tomography (LDCT) screening for individuals 50-80 years old who have a smoking history $\geq 20$ pack-years and are either current smokers or have quit within 15 years. The two major RCTs of LCS for high-risk subjects with a smoking history established diagnoses of lung cancer in 1.05% and 0.9% of the screened group, respectively\(^2,3\).

Although smoking is the major risk factor, the proportion of never-smokers among lung cancer patients in the USA has increased alarmingly, from 8% in 1990-1995 to 12.5-12.7% in 2016-2018\(^4,5\). Notably, this proportion rises to 15.7% in females compared to 9.6% in males (9.6%)\(^5\) and is strikingly high in females of certain Asian ethnic groups (52.7% to 85.7%)\(^6\). The focus of the current screening criteria on smoking history disqualifies light smokers and never-smokers who may have other substantial risk factors for lung cancer, dramatically reducing the chance of early detection in these individuals.

The proportion of never-smokers among lung cancer cases, and the number of overall cases in never-smokers, is especially high in Asian/Asian-American females\(^6\). USPSTF criteria have been shown to miss over 75% of lung cancers in Asians and Asian-Americans\(^7,8,9\). With most Asian females who develop lung cancer being never-smokers, this subgroup is fully
excluded from LCS in the US. The USPSTF-2021 recommendation does acknowledge the
insufficiency of the current criteria for some racial groups, making a special mention of Black
men and Latino/Hispanic people, but it makes no mention of Asians/Asian-Americans.

What is the incidence of lung cancer in Asian non-smokers?

Due to a lack of RCTs in this subgroup, risk factors that might render never-smokers of
Asian ancestry particularly susceptible to lung adenocarcinoma remain largely unknown. A few
Asian nations have evaluated broadening the criteria for eligibility for LCS. The Taiwan Lung
Cancer Screening for Never smoker Trial (TALENT) study\textsuperscript{10} is one such example. This was a
targeted, multi-center LCS trial in never-smokers 55-75 years of age with any one of the
following risk factors: family history of lung cancer, passive smoking exposure, history of
tuberculosis/COPD, cooking index\(\geq 110\), or not using a ventilator while cooking. 17.4%
(2094/12011) of screened patients were “screen-positive”, of whom 392(3.3\%) underwent an
invasive procedure, either biopsy/surgery. Among these, 257(65.5\%) and 61(15.5\%) were found
to have invasive and non-invasive lung cancer, respectively, whereas the remaining 74(18.8\%)
were deemed benign/non-lung cancer malignancy. Of the entire screened group, 2.1\% had
invasive lung cancer (compared to 1.05\% and 0.9\% in the National Lung Cancer screening Trial
(NLST) and the NELSON trial, respectively). Importantly, the incidence of invasive cancer was
significantly higher in never-smoking females (NSF) compared to never-smoking males (2.4%
vs. 1.4\%, \textit{p}=0.001) (Personal communication with Dr. Yang PC, Principal Investigator).

A trial from mainland China\textsuperscript{11} randomized participants 50-75 years of age with at least
one of the following risk factors-- \(\geq 30\) pack years and within 15 years of quitting, non-smokers
exposed to passive smoking (home/workplace) for ≥20 years, and non-smokers with a family history of lung cancer. These individuals were randomized to three groups: No intervention; LDCT at baseline, 1-year, and 2-years; and LDCT at baseline, 1-year, and 3-years. In both LDCT groups combined, the incidence of lung cancer, including non-invasive cancers, was 1.8% at baseline, compared to 1% if the USPSTF 2021 criteria alone were applied to the cohort. It is noteworthy that the incidence rate of lung cancer in females was 4.2%, compared to 0.7% in males. Moreover, the incidence rate among NSF was 4.1%. Although the data is limited, Asian NSF with certain risk factors do appear to have a higher baseline risk of developing lung cancer.

Some have questioned whether the above Chinese/Taiwanese data are directly applicable to ethnic Chinese reared/living in the USA due to environmental exposures in Asia that may not exist in the USA. However, a study conducted among Chinese males and females in the USA diagnosed with lung cancer between 1990 and 2004 that looked at incidence trends by immigration status revealed that the incidence of lung cancer declined with time among foreign-born Chinese-American males but not Chinese-American females. In addition, incidence rates of squamous cell carcinoma in Chinese-American females decreased with time, but adenocarcinoma rates remained constant. Adenocarcinoma is, of course, the predominant type of lung cancer in NSF. Hence, Asian-American NSF appear to have a similar risk of lung cancer as Asian NSF.

**What is the incidence required in a population for LCS to have benefit?**

Although there is no agreed-upon risk threshold for which LCS is indicated, the National Comprehensive Cancer Network (NCCN) has suggested 1.3% absolute risk as a criterion for
LCS\(^{13}\). The cumulative lung cancer incidence rates of 1.1\% (over 6 years) and 0.9 \% (over 10 years) in LCS trials -- NLST and NELSON\(^{2,3}\), respectively, were sufficient to result in a mortality benefit of 20-24\% with screening\(^{2,3}\). Moreover, a risk factor model (PLCO\(_{m2012}\)) from the Prostate, Lung, Colorectal, and Ovary (PLCO) cancer trial data found that a lung cancer incidence threshold of only 0.015 was required to gain a 20\% mortality benefit from LCS\(^{14}\). Admittedly, these threshold suggestions are based upon the prognosis of predominately smoking-related lung cancers. Nevertheless, the implementation of an LCS program in never-smoking Asian-Americans with additional risk factors would at least seem worthy of careful consideration, given the 2.1\% incidence of invasive lung cancer in the TALENT trial.

**Which Asian ethnicities are at high risk?**

An estimated 18.9 million Asians\(^{15}\) are residing in the USA, consisting of 12 million (63\%) females, with 92.7\% of them being never-smokers\(^{16}\). The Asian immigrant group is the fastest-growing and is expected to become the largest, surpassing Hispanics by 2045\(^{17,18}\). The Asian-American community has origins in a variety of cultural and racial backgrounds, and combining these groups that may have varying cancer risk profiles can result in loss of crucial information regarding the group-specific predisposition to lung cancer. Among Asian-American NSFs, only one group does not appear to have an incidence higher than White-American NSFs: Japanese-American NSFs have an age-adjusted incidence rate (AAIR) of 6.4(95\%CI;3.6-10.0) per 100,000 patient-years compared to 10.1(95\%CI;9.0-11.3) in non-Hispanic White NSFs and 8.5(95\%CI;5.7-11.8) in Hispanic White NSFs. NSFs from other Asian-American ethnicities showed a significantly higher AAIR of lung cancer-- 22.8(95\%CI;17.3-29.1) in Chinese-
American NSFs, 20.1 (95% CI: 14.1-27.1) in Filipinx-American NSFs, and 20.3 (95% CI: 13.4-28.5) in other Asian-American NSF groups combined (Indians, Vietnamese, Koreans)\textsuperscript{19}.

What other risk factors might be considered in selecting never-smoking Asian females for screening?

While based upon the above information, there may be a basis for screening Asian-American females, additional risk factors beyond race that might be targeted remain incompletely identified. Most LCS studies that included Asian NSFs showed the average age at lung cancer detection to be 55-61 years\textsuperscript{10,11,20,21}. That age is a factor is also suggested by the relatively low incidence rate (0.7%) detected in the largest LCS study in China--a study that included a considerable (~25%) proportion of subjects between 40-50 years\textsuperscript{22}. It would appear, therefore, that screening Asian-American females under 50 years of age is unlikely to yield substantial invasive lung cancer detection. Given the sometimes-indolent nature of lung cancers detected in this population, which we will discuss in more detail in the later sections, it may well prove appropriate to adjust the upper age limit of screening to 75 years rather than 80 years for this specific population.

LCS trials in never-smoking Asian populations also showed a high incidence of lung cancer in individuals with a family history of lung cancer in the first-degree (3.2%), second-degree (1.7%), and third-degree (1.6%) relatives\textsuperscript{10,20,23}. Other risk factors, such as history of passive smoking $\geq$20 years, have also been demonstrated to have a higher incidence of lung cancer in NSFs\textsuperscript{11}.
Although NCCN, American College of Chest Physicians (CHEST), and American Association for Thoracic Surgery (AATS) have suggested the use of risk-factor models to target groups not covered by the current USPSTF-criteria, even the best-calibrated risk-factor models, such as the PLCO$_m^{2012}$ and LCRAT have fared poorly in never-smokers. The never-smoker-specific risk-models (PLCO$_{all}^{2014}$, NCC-LC$_m^{2021}$), based on prospective data, showed a significant improvement in detection of lung cancer and number needed to screen to prevent mortality. However, despite having accounted for several risk-factors (body mass index, history of COPD, socioeconomic status, personal history of cancer, and family history of lung cancer), they still underperformed in predicting lung cancer in Asian never-smokers (AUC=0.67-0.69)$^{24,25}$. This indicates that there are risk factors that remain unidentified and unaccounted for. It is likely that these are inherited risk factors.

**The possible problem of overdiagnosis (and other risks of screening)**

Although screening Asian-American NSFs has the potential to decrease mortality, this possible benefit must be balanced against the potential risks. Some of the most important issues that could inappropriately increase risks of cancer screening are: 1) a high false positive rate (FPR) resulting in resection of an excessive number of benign lesions; 2) the risk of “overdiagnosis” – i.e., identifying a large number of preinvasive/minimally invasive lesions that might never have impacted patient longevity if left undiscovered and untreated; 3) cumulative radiation exposure from repeated LDCTs; and 4) anxiety associated with screen positives that are managed with prolonged monitoring.
The baseline FPR per screening round in the NLST and the NELSON trials were 26.3%\(^2\) and 19.8%\(^3\), respectively. However, application of Lung-Reporting and Data System (Lung-RADS) for the diagnosis of suspicious nodules to the same NLST population demonstrated a decrease in the FPR from 26.6% to 12.8%\(^6\) resulting in a decline in benign resection rates to as low as 0.43-6.2%\(^{27,28}\). Thus, in the currently screened population, at least, rates of benign resections should now be sufficiently low as to not pose a major concern.

More relevant to potentially implementing screening in Asian never-smokers is the possible problem of overdiagnosis— the increased detection of subsolid nodules (pure ground glass nodules (GGN) and part-solid/heterogeneous nodules) that, while “neoplastic,” could be argued to have an uncertain influence on patient outcomes. It is almost certainly true, given the greater incidence of subsolid tumors on the adenocarcinoma spectrum among Asian never-smokers vs. smokers, that this issue of identifying many very low-grade malignancies on LCS has the potential to be a bigger problem in never-smoking Asians than in others. Indeed, many EGFR-mutation-driven adenocarcinomas in Asian never-smokers either originate as a pure GGN or have a ground glass component\(^{29}\).

Lung-RADS version 1.1\(^{30}\), a consensus statement by the American College of Radiology, is widely used to guide the management of screen-detected nodules. Although it has good accuracy for predicting invasive cancers in solid nodules, a study by a group from Brigham and Women’s Hospital on the validation of Lung-RADS for subsolid nodules detected in the NLST demonstrated that Lung-RADS underestimated the risk of invasive lung cancer in categories 2, 3, and 4A, which based on the study were 3%, 14%, and 23% in contrast with the Lung-RADS estimates of 1%, 2%, and 15%, respectively\(^{31}\). It has also been shown that Lung-RADS 1.0 is not as good a predictor of invasive lung cancer in screen-detected nodules for Asians compared to...
non-Asians. Clinicians should, hence, be wary of the potential underestimation of the risk of invasive lung cancer in screen-detected subsolid nodules among the Asian-American population when employing Lung-RADS. That being said, these lung cancers in these subsolid nodules do tend to be more indolent than those detected in solid nodules.

Stage 0 adenocarcinoma, which usually appears radiographically as a pure or heterogeneous GGN, represents a pre-invasive neoplastic lesion, either atypical adenomatous hyperplasia (AAH) or adenocarcinoma in-situ (AIS). The need for resection of these stage 0 lesions has been questioned given the 100% rate of 5-year and 10-year recurrence-free survival post-resection. However, it is well known that in many cases, these pre-invasive lesions progress to invasive tumors (appearance of a solid component on CT correlating highly with progression to MIA/lepidic predominant adenocarcinoma), sometimes even after a latency of ten years. This progression appears to occur in at least 6% and 14% of pure and heterogeneous GGNs, respectively, over 5 years, according to a prospective study. The median time to development of solid component in the pure and heterogeneous nodules was 3.8 and 2.2 years, respectively. A few other retrospective studies in the Asian population on the natural history of pure GGNs demonstrated progression (defined as growth ≥2mm growth in the diameter of the nodule or appearance of a solid component) ranging from 13-19%, 15-32%, 19.6-27%, and 9.8%-30% at a median follow-up of 2, 3, 4, and 5 years, respectively. Particularly, the appearance of solid component was demonstrated in 6.3% and 7.7% of pure GGNs with a mean nodule size of 8.3mm (range, 3-17) and 7.8±4.4mm (mean±SD). While the most consistent predictors of growth in pure GGNs included initial size >10mm and a history of lung cancer, the predictors of the appearance of solid component remain undefined. Moreover, studies on the natural history of pure nonsolid nodules after an initial
stable period of 3 and 5 years stilled progression of nodules in 3.3\%^{E12} after 3 additional years and 2.1\%^{E13} after 5 additional years of follow-up, respectively. While there is a consensus that resection is, in most cases, indicated upon progression to the invasive stage, one group estimated that resection of adenocarcinomas, even at the pre/minimally invasive stage, results in a gain in life years of 10.8 years, despite adjusting for a lead time of 4.6 years^{34}.

The rate of stage 0 tumors was not reported in the NLST and NELSON trials due to the lack of existence of this nomenclature during that period. However, they reported “overdiagnosis” rates of 18.5\% and 8.9\%^{E14}, respectively, though defined as detection of cancers by LDCT that would not have been detected by chest X-ray during the trial-defined follow-up period. On the other hand, the TALENT study\textsuperscript{10} and Chinese LCS trial\textsuperscript{11}, reported an 18.5\% and 45.4\% rate of pre-invasive/stage 0 (AIS) lung cancer identification, respectively. A retrospective study from South Korea on LCS\textsuperscript{E15} in patients without any risk factors showed that out of the 227 screen-detected lung cancers, 31 (13.7\%) were preinvasive (AIS), whereas the rest were MIA/IAC, similar to rates of preinvasive cancer (18.86\%\textsuperscript{8} and 47\%\textsuperscript{20}) from other Asian studies. Although this is relatively high, it is clear that most GGNs with a solid component (MIA), and at least a substantial subset of pre GGNs (AIS/AAH) will eventually progress to invasive adenocarcinoma (IAC)\textsuperscript{E16}. In fact, Asian descent\textsuperscript{E17} and family history of cancer\textsuperscript{E1} have been associated with early progression to invasiveness in the preinvasive forms of adenocarcinoma. Additionally, EGFR-mutation-driven cancers exhibit a higher (90\%) rate of progression compared to non-EGFR mutation-driven cancers (20\%)\textsuperscript{E1}; and 74\% of lung cancers in the non-smoker Asians are due to EGFR mutations\textsuperscript{E18}. It does, however, remain to be defined if this considerable rate of progression to IAC offsets the risk of overdiagnosis.
On the same note, the widespread promotion of LCS in Taiwan since 2004 has been criticized with regard to overdiagnosis, as there was an increase in the incidence of early-stage (stage 0-I) lung cancer (2.3 to 14.4 per 100,000 population) from 2004 to 2018 that was not accompanied by a decline in the incidence of stages II-IV lung cancer (18.7 to 19.3 per 100,000 population). However, in contrast to that finding, another study demonstrated that not only was there a stage shift in the incidence of lung cancer from late (III/IV) to early (I/II) stages, but that this was associated with a more than doubling in survival. This latter study also noted a decrease in the annual percent change in overall mortality after the onset of screening from 0.41% to -2.41%.

Although concerns have been raised regarding cumulative radiation exposure with LCS, LDCT utilized for screening has 90% lesser ionizing radiation exposure than a conventional diagnostic chest CT scan, and the estimated lifetime risk of major cancers is no more than 0.26-0.81 for every 1000 people screened with the cumulative exposure of 10 annual LDCTs. Additionally, while some studies have shown no additional risk of worse health-related quality of life or anxiety state in those who receive false positive or incidental LDCT screening findings compared to those with negative findings, other studies showed negative psychosocial effects, although they were short-lived and soon returned to baseline, even after false-positive and indeterminate results. In our view, the benefit of LCS in this population is very likely, assuming a low rate of complications from treatment, based simply upon the high rate (90.9-96.5%) of detection of neoplasms in early stages (0-I), rendering these highly curable.

It is clear that 2.1-2.4% of the screened Asian NSF population is detected with invasive lung cancer, most of which present as part-solid nodules, in addition to a proportion that presents as pure GGNs, among which approximately ~10% develop a solid component (or ~20-
30% show growth) over time, necessitating surgical resection (or radiation) to mitigate the risk of life-threatening disease. It is true that these part-solid IACs generally demonstrate a more indolent nature than solid, smoking-associated non-small cell lung cancers. However, there is little doubt that most will progress to a potentially metastatic state over several years. Although it is not entirely clear if resection of such low-grade, invasive malignancies will impact survival, it seems likely that it will. Certainly, it is crucial to adopt a nuanced approach to this topic, with prioritization of targeted strategies for screening and only selective intervention for screen-detected nodules, to reduce unnecessary procedures and associated healthcare burden.

Conclusions

The incidence of lung cancer in Asian-American NSFs is high and a cause for concern. The issue is further exacerbated when one considers the existing disparities between White Americans and Asian-Americans in the diagnosis and early management of lung cancer\textsuperscript{E25} and the low overall uptake of screening in general within this population\textsuperscript{E26}. We believe that additional studies should be undertaken urgently in the USA to determine definitively if Asian-American NSFs should be considered a high-risk group and be recommended to undergo LCS by LDCT. The many pre-invasive and MIA tumors that will be identified can then be addressed with conservative follow-up imaging protocols based upon recent and emerging guidelines for the approach to subsolid nodules\textsuperscript{E27}. Few of these will require early resection, while at the same time, appropriate follow-up will allow very few to progress to invasive cancer before curative treatment can be undertaken. It is possible that the tendency toward lower-grade tumors in Asian-American NSFs will dictate that LCS be initiated at a later age and/or terminated at an earlier age than in current guidelines for patients with a smoking history.
We are aware of two studies-- the Female Asian Never Smoker (FANS) Study through University of California San Francisco and the Female Asian Non-smoker Screening Study (FANSS) through New York University-- that are underway and are designed to address some of the issues presented herein. Although their anticipated completion dates are years in the future, the interim results of the FANSS presented recently at the American Society of Clinical Oncology-2023 and the International Thoracic Surgical Oncology Summit-2023 meetings. These results are consistent with other Asian studies cited above and found a higher rate of invasive lung cancer than did the NLST – they showed a 1.5% (3/201) incidence of invasive lung cancer (all IIB and above) in at-risk female Asian-American never-smokers, and a ~5% rate of >5mm GGOs [Personal communication with Dr. Shum]. However, it is likely that more than these two studies alone (only one being a pure, prospective screening study), with larger sample sizes, will be required to provide convincing evidence regarding a survival benefit of screening for these neoplasms. In fact, it is likely that randomized data will be required. It is our strong belief that ongoing and future work in this area will provide the required data to apply LCS to Asian-American NSFs, ultimately further reducing lung cancer mortality. At a minimum, we hope that the data presented herein will focus the attention of clinicians and researchers more acutely on this population.

Journal Pre-proof
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Hi Dr. Devanish,

I apologize for the delay to respond to your email. Please see attached for the presentation I gave at ITLOS.

Thanks,
Elaine
Pan-Chyr Yang <panchyryang@gmail.com>
To: Devanish Narasimhasanthy Kamtam

Dear Dr. Devanish:

Thanks for the message. The TALENT team permits your use of our unpublished work.

Best wishes,

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